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EXAMINER	
SAIDHA, TEKCHAND	

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Commissioner for Patents

Examiner's Answer to the Appeal Brief filed 4/20/2006 is enclosed.

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BEFORE THE BOARD OF PATENT APPEALS

AND INTERFERENCES

Application Number: 09/839,946

Filing Date: April 19, 2001

Appellant(s): WILLIAMS ET AL.

Brian J. Del Buono

For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed April 20, 2006 appealing from the Office action mailed 7/20/2005 (Final rejection) and 12/05/2005 (Advisory).

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

Lee et al., Science 239: 1288-1291 (1988) cited by Appellants in the First Supplemental Information Disclosure Statement filed November 14, 2002 as document AT14 and cited by the Examiner in

the Office Action mailed September 11, 2003. (Cited by Appellants in Brief).

Conley et al., J. Biochem. 187: 727-732 (1980) cited by the Examiner in the Office Action mailed July 20, 2005. (Cited by Appellants in Brief).

T.G. Conley and D.G. Priest, Preparative Biochemistry 9:197-203 (1979) cited by Appellants in the Amendment and Reply Under 37 C.F.R. § 1.111 filed November 2, 2004. (Cited by Appellants in Brief).

Declaration Under 37 C.F.R. 1.132 by Merry R. Sherman, Ph.D., filed with Appellants' Amendment and Reply Under 37 C.F.R. § 1.111 on May 26, 2005 and acknowledged by Examiner in the Office Action mailed July 20, 2005. (Cited by Appellants in Brief).

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 50-53 are rejected under 35 U.S.C. § 102(b) as anticipated by Lee et al. [Science 239, 1288-1291 (1988), IDS, previously cited].

Lee et al. (1988) teach the *recombinant* production of full length amino acid sequence of porcine Urate oxidase (also known as uricase)(*see* abstract lines 8-10) which is tetrameric and is substantially pure. Mammalian uricase is disclosed as a tetramer with subunit size of 32,000 daltons (page 1288, column 2,first paragraph after the abstract). The reference further teaches purification to **homogeneity** of Porcine and murine urate oxidase (see, page 1289, column 2). The reference on page 1290 identifies a 2.2-kb cDNA, which is an authentic clone for porcine urate oxidase. Oxidation of uric acid to allantoin is catalyzed by urate oxidase (see abstract). Increased uric acid level, due to lack of this enzyme in man can lead to gouty arthritis (page 1288, column 2).

Appellants' claims are directed to 'tetrameric mammalian uricase, wherein at least about 90% of said uricase is in

tetrameric form' and less than about 10% of said uricase is in non-tetrameric aggregated form. This is interpreted here to mean that more than 90% may also be present in the tetrameric form. More than 90% may also mean 100% or homogenous preparation. Less than about 10% of said uricase is in non-tetrameric aggregated form, may also mean 0% in non-tetrameric form or homogenous preparation. Therefore, the homogenous preparations of porcine or murine tetrameric uricase disclosed by Lee et al. is no different than the claimed uricase. The reference therefore anticipates the claims.

(10) Response to Arguments

A. Claims 50-53 Are Anticipated by Lee

Appellants argue that Examiner relied on Lee as allegedly teaching an isolated tetrameric mammalian uricase, wherein at least about 90% is in tetrameric form' and less than about 10% of said uricase is in non-tetrameric aggregated form. Applicants argue that Lee does not teach every element recited in claims 50-53. Therefore, the Examiner's rejection of claims 50-53 based on 35 U.S.C. 102(b) over Lee is legally and factually unfounded.

To establish a *prima facie* case of anticipated under 35 U.S.C. § 102(b), the Examiner must that "each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference".

Verdegaal Bros. v Union Oil of California, 814 F2d 628, 631 (Fed. Cir. 1987). *See also Kalman v. Kimberly Clark Corp.,* 713 F.2d 760, 771 (Fed. Cir. 1983) *cert denied,* 465 U.S. 1026 (1984). Because the Examiner has failed to establish that each and every element of the claims 50-53 is described, either expressly or inherently, in Lee, this rejection of claims must be reversed.

Appellants arguments are considered but not found to be persuasive because in general anticipation law requires distinction be made between invention described or taught and invention claimed; it does not require that reference "teach" what subject patent teaches; assuming that reference is properly "prior art," it is only necessary that claims under attack, as construed by court, "read on" something disclosed in reference, i.e., all limitations of claim are found in reference, or are "fully met" by it. Therefore, based upon this general principle, and explained above, the reference does teach all claim limitations as explained by the claim interpretation in the anticipation rejection.

B. Lee Does Expressly Disclose Each And Every Element of claims 50-53

Appellants' argue that Examiner interpreted a homogeneous preparation of uricase in Lee to encompass a preparation in

which at least 90% of the uricase is in tetrameric form. *See* Final Office Action mailed July 20, 2005 at pages 3-4. Furthermore, the Examiner pointed to a statement in Lee that mammalian uricase "exists as a tetramer with an apparent subunit size of 32,000 Daltons" to support his contention that the mammalian uricase disclosed in Lee was 100% in the tetrameric form. Appellants respectfully disagree with these contentions, and with this interpretation of Lee upon which these contentions are based, for at least the following reasons.

1. First, lee does not expressly disclose the purification of tetrameric mammalian uricase as recited in the claims of the present application. Lee only indicates that porcine liver and murine urate oxidase were purified to homogeneity. Lee does not indicate that **at least** 90% of the purified uricase was in a tetrameric form. Indeed, Lee does not indicate that in *what* form the purified uricase was, let alone that at least 90% of it was in a tetrameric form.

2. Second, while the Examiner was correct in his assertion that mammalian uricase has a tetrameric structure (as disclosed in the Lee reference), Appellants respectfully point out that is not the same as isolated uricase being in a non-aggregated tetrameric form (as claimed in the present invention. Applicants further arguments emphasize how based upon the

instant, page 16, lines 5-16, how the estimated percentage of non-tetrameric aggregated form of the enzyme varied from 10% to about 80%.

It is noted in Appellants' response that the mammalian uricase has a tetrameric structure and is disclosed in the Lee reference. *See* page 10 of the 'Brief' and the foot note to Conley's reference. While it true that Lee reference does not expressly disclose that the isolated tetrameric mammalian uricase, is at *least* about 90% is in tetrameric form' and *less than* about 10% of said uricase is in non-tetrameric aggregated form. However, the claims when given the broadest reasonable interpretation, as is given here, in which case the limitation "at *least* about 90% is in tetrameric form", would also mean that "more than 90% may also be present in the tetrameric form. **More than 90% may also mean 100% or which is same as homogenous preparation. Less than about 10% of said uricase is in non-tetrameric aggregated form, may also mean 0% in non-tetrameric form or homogenous preparation.** Therefore, the homogenous preparations of porcine or murine tetrameric uricase disclosed by Lee et al. is no different than what is being claimed. Therefore, the claims are anticipated by the cited art.

Appellants in explaining Lee et al., point that Examiner contends that Lee discloses the recombinant production of full

length amino acid sequence of porcine Urate oxidase (uricase) which is tetrameric and is substantially pure. Mammalian uricase is disclosed as a tetramer with subunit size of 32,000 daltons (page 1288, column 2,first paragraph after the abstract). The reference further teaches purification to **homogeneity** of Porcine and murine urate oxidase (see, page 1289, second column). Appellants respectfully disagrees with this interpretation for the following reasons.

Lee does not expressly disclose the purification of tetrameric mammalian uricase as recited by the claim of the present application. This reference only indicates *in passing* that the porcine liver and murine urate oxidase were purified to homogeneity. The reference does not indicate that at least 90% of the purified uricase was in tetrameric form. Indeed, the reference does not indicate in what form the purified uricase was, let alone that at least about 90% of it was in a tetrameric form.

From the article [Lee et al.] and from the explanation, it is amply clear that the art as applied anticipates the claims. First of all, the art cited clearly points to the fact that the mammalian uricase is disclosed as a tetramer with subunit size of 32,000 daltons (page 1288, column 2,first paragraph after the abstract). This is also well documented in Appellants' own

specification on page 3, line 15, citing Wu et al. [PNAS USA 86: 9412-9416, 1989].

Regarding Appellants' arguments that Lee's reference only indicates *in passing* that the porcine liver and murine urate oxidase were purified to homogeneity is without basis, and is distorting the facts presented in a well known and reputed scientific journal such as 'Science'. Further, as explained in the 102 rejection, at least 90% of the uricase was in tetrameric form, is encompassed by the homogeneous preparation, and is no different than what is claimed.

Applicants citing Conley et al. [Preparative Biochemistry 9:197-203 (1979)] argue that Conley report that the 'enzyme is homogeneous upon polyacrylamide gel electrophoresis in the presence of Sodium dodecyl sulfate [see Conley at p. 201]. Applicants further argue that one of ordinary skill in the art would immediately recognize, the conditions of SDS/PAGE employed by Conley (and therefore Lee) dissociate any uricase tetramer that might be present into the smaller 32-33 kDa monomeric subunits. As disclosed in the present specification at page 16, lines 5-7, tetrameric uricase is 140 kDa protein. Hence, Conley (and therefore Lee) clearly is identifying monomeric forms of uricase, rather than tetrameric forms of uricase.

Appellants' explanation is not found persuasive because - in a denaturing gel such as SDS/PAGE, only the subunit form of the uricase is evident. Since all the 4-subunits are of the same size, the uricase appears/migrate as a single band on a SDS/PAGE. Since each subunit is approximately 32-33kDa, the native tetrameric form of the uricase in question would be 33X4=132 kDa, which is good estimate for molecular weight determination, and is within a reasonable range to that disclosed by the Appellants. Therefore, the homogeneous preparation of Lee et al. is not distinct to that claimed by the Appellants. No inherency argument is deemed necessary as the claims are not drawn to any specific SEQ ID No., and because Conley's work further support Examiner's use of Lee et al. in 102 rejection.

Appellants' attention is also drawn to Conley et al. [Biochem. J (1980) 187, 727-732, IDS], at page 727, column 1, lines 1-3, where Uricase from pig liver consists of four apparently identical subunits. Table 2. further teaches the physical properties of pig uricase and define the molecular weight to be 125,000, with the subunit size of 32,000. Four identical subunits as defined by the Conley reference (1980) will further clarify that the uricase is tetrameric [four subunits].

Appellants citing their reply filed on December 11, 2003, at pages 26-28 (*see* page 12 of the Appellant Brief), argue that "uricase preparations such as those available from Sigma (including Sigma Cat. No. U 3250, the particular commercially available uricase used in the studies in Lee) contain substantial quantities (i.e. more than about 10%) of non-tetrameric form of the enzyme. Put another way, Sigma uricase used in Lee does not contain uricase in which at least about 90% of the uricase is in tetrameric form, as required by the present claim."

The arguments having been considered are not found to be persuasive because the Appellants have provided no concrete evidence or data about the composition of Sigma uricase(s). For argument sake, even if the composition of the Sigma uricase is what the Appellants are claiming it be, the Sigma uricase was used in the work of Lee for further purification.

Appellants further argue that 'This contention is supported by the present specification which discloses that a commercial preparation of uricase, also obtained from Sigma, had to be purified by the methods of the present invention in order to obtain the tetrameric form of the uricase. *See* specification at page 20, lines 9-13."

Appellants specification, page 20, lines 6-8, disclose size exclusion HPLC purification used in the identification of fractions of the eluates containing the desired tetrameric form of the uricase to be free of **'any detectable aggregates'**. This is quite contrary to Appellants' claims directed to tetrameric uricase... where in less than 10% of said uricase is in non-tetrameric aggregated form.

Appellants further support their conclusion based upon the Declaration of Merry R. Sherman (Exhibit D, pages 40-44 of the Brief).

Declaration of Merry R. Sherman Under 37 C.F.R. 1.132 (Arguments)

Appellants' support their conclusion by the data presented in the "Declaration of Merry R. Sherman Under 37 C.F.R. 1.132", and argue that these data clearly show that isolated preparations of natural and recombinant uricase, such as those prepared by the methods of Lee, contain multiple forms of the uricase, including octomers and larger aggregates. Appellants further argue that as 'shown in Figures 1 & 2 (top panel) of the Sherman declaration, the octomers and larger aggregates (or non-tetrameric) account for greater than about 10% of the uricase present in these preparations (see page 3, paragraph 8 of the Sherman Declaration; or page 42 (paragraph 8) of the brief).

This is contrary to Appellants' language in claim 50, wherein the claim recites 'less than about 10%..in non-tetrameric form' (*see* Appellants response, page 8, lines 10-18). This is further complicated by Appellants statement in the an earlier reply (*see* Appellants' arguments filed 5/26/2005, Remarks page 8, page 8, lines 6-8), wherein the non-tetrameric aggregated form of the enzyme present in such 'purified' preparations varies from more than 10% to about 80%. Therefore, base upon the diverse range of aggregations as a result of mammalian uricase purification, reported in the instant specification as well as the declaration of Merry R. Sherman, it is quite clear that there is enormous variations in the composition of uricase purified depending upon perhaps the buffers, dilutions, source and so on, and that the aggregation is the inherent property of the enzyme in solution or that the different forms of the uricase (tetrameric or non-tetrameric) may aggregate differentially depending upon the concentration of protein in solution. Therefore the added limitation of 'less than about 10% of said uricase is in a non-tetrameric aggregated form' is neither well supported nor should carry weight to the patentability of the claims.

C. ***Examiner has not Relied upon Inherent Anticipation***

Claims 50-53 are rejected under 35 U.S.C. § 102(b) as anticipated by Lee et al. [Science 239, 1288-1291 (1988), IDS, previously cited].

As indicated above this is not an inherent anticipation rejection since the broad claims are not drawn to any specific SEQ ID No.

Appellants' arguments on page 15, lines 6-11 of the Brief recite "Since Lee does not disclose how one of ordinary skill in the art might take the homogeneous isolated monomeric preparations of uricase disclosed in that reference, and produce isolated tetrameric uricase from those monomers, this reference does not enable one of ordinary skill to make the subject matter of the presently claimed invention. Accordingly, for at least these reasons, and under *Donohue and PPG Industries* [*In re Donohue*, 766 F 2d 531, 533 (Fed. Cir. 1985); and *PPG Industries, Inc. v. Guardan Industries Corp.*, 75 F.3d 1558, 1566 (Fed. Cir. 1996)], Lee cannot and does not anticipate the present claims.

Appellants arguments are scientifically flawed and therefore legally baseless at least for the following reasons:

Lee isolated uricase preparation is not monomeric as per Lee et al., Science 239: 1288-1291 (1988), and as explained in the rejection, as well as admitted by the Appellants in their own arguments. It is noted in Appellants' response that the

mammalian uricase has a tetrameric structure and is disclosed in the Lee reference. *See* page 10 of the 'Brief' and the foot note to Conley's reference.

Mammalian uricase is disclosed as a tetramer with subunit size of 32,000 daltons (page 1288, column 2,first paragraph after the abstract). The reference further teaches purification to homogeneity of Porcine and murine urate oxidase (see, page 1289, second column).

Therefore Appellants contention that Lee's uricase is monomeric has no support either in Lee's reference or in their earlier arguments noted above.

Perhaps Appellants' confusion that Lee's uricase is disclosed as 'monomeric' is due to a lack of clear understanding of the migration of the 'tetrameric uricase' in a non-denaturing or native gel as against SDS/PAGE denaturing gel. This has been discussed and explained above (*see* page 9).

D. *Lee Does Expressly Or Inherently Disclose Each and Every Element of Claims 50-53.*

Citing *Kalman v. Kimberley Clark Corp.*, 713 F.2d 760, 771 (Fed. Cir. 1983), *cert. denied,* 465 U.S. 1026 (1984), Appellants argue that a claim can be anticipated only if every element in the claim is expressly or inherently disclosed in a single prior art reference.

As explained before it is noted in Appellants' response that the mammalian uricase has a tetrameric structure and is disclosed in the Lee reference. *See* page 10 of the 'Brief' and the foot note to Conley's reference. While it true that Lee reference does not expressly disclose that the isolated tetrameric mammalian uricase, is at *least* about 90% is in tetrameric form' and *less than* about 10% of said uricase is in non-tetrameric aggregated form. However, the claims when given the broadest reasonable interpretation, as is given here, in which case the limitation "at *least* about 90% is in tetrameric form", would also mean that "more than 90% may also be present in the tetrameric form. More than 90% may also mean 100% or which is same as homogenous preparation. Less than about 10% of said uricase is in non-tetrameric aggregated form, may also mean 0% in non-tetrameric form or homogenous preparation. Therefore, the homogenous preparations of porcine or murine tetrameric uricase disclosed by Lee et al. is no different than what is being claimed. Therefore, this reference can support the rejection under 35 U.S.C. § 102(b) for teaching all the claim limitations in a single prior art.

For the above reasons, it is believed that the rejection should be sustained.

Respectfully submitted,

Tekchand Saidha
Primary Examiner, Art Unit 1652
July 3, 2006

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